Ugi-Smiles couplings of purine derivatives.


Experimental:

$^1$H NMR spectra were recorded on a Brucker Avance 400 MHz spectrometer, using CDCl$_3$ as solvent. $^{13}$C NMR spectra were recorded on a 100.6 MHz spectrometer. Chemical shifts are reported in ppm relative to internal TMS. Coupling constant $J$ is quoted in hertz Hz. IR spectra were performed on a Perkin-Elmer FT 1600 spectrometer. High-resolution mass spectra (HRMS) were carried out with JEOL Gcmate spectrometer. Melting points (mp) were determined on a Stuart SMP3 apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on silica gel using precoated plates of silica 60 F$_{254}$.

General procedure for Ugi-Smile coupling reaction:

To solution of aldehyde (1.0 mmol) in DMF/MeCN (0.6 mL, 1:2, 1.6 M) was added, under argon atmosphere, amine (1.0 mmol), 6-mercaptopurine (1.0 mmol) and, isocyanide (1.0 mmol) respectively. The reaction contents were stirred and heating at 60°C for several hours. The progress of the reaction was monitored by TLC. After completion of reaction (time given in Table 1), the solvent was removed under reduced pressure and the crude reaction mixture was purified by flash column chromatography to afford the desired product.
2-(allyl(9H-purin-6-yl)amino)-N-cyclohexyl-4-methylpentanethioamide 2a

![Chemical Structure](image)

\[ \text{C}_{20}\text{H}_{30}\text{N}_{6}\text{S} \]

Mol. Wt. = 386.557 g.mol\(^{-1}\)

This compound was synthesized according to the general procedure, using isovaleraldehyde (108 µl, 1.0 mmol), allylamine (75 µl, 1.0 mmol), 6-mercaptopurine (152 mg, 1.0 mmol) and cyclohexyl isocyanide (125 µl, 1.0 mmol). The desired product was isolated in 58% yield (224 mg, 0.580 mmol) after purification by flash column chromatography on silica gel using (10:90 Ethyl acetate/ Dichloromethane) as eluent.

**Nature:** White Solid

**M.P.** = 185-186°C

**Rf:** 0.4 (40:60 Ethyl acetate/ Dichloromethane)

**NMR \(^1\text{H}\) (CDCl\(_3\), 400 MHz):** \(\delta\) 10.38 (br s, 1H, NH), 8.46 (s, 1H), 8.06 (s, 1H), 6.44-6.30 (m, 1H), 6.03 (ddd, \(J = 15.9, 10.1, 5.1\) Hz, 1H), 5.21 (d, \(J = 17.1\) Hz, 1H), 5.10 (d, \(J = 10.2\) Hz, 1H), 4.86-4.83 (m, 1H), 4.59-4.56 (m, 1H), 4.33-4.31 (m, 1H), 2.09-2.06 (m, 3H), 1.71-1.67 (m, 2H), 1.62-1.49 (m, 3H), 1.43-1.30 (m, 3H), 1.24-1.17 (m, 2H), 0.92 (d, \(J = 6.5\) Hz, 3H), 0.85 (d, \(J = 6.3\) Hz, 3H).

**NMR \(^{13}\text{C}\) (CDCl\(_3\), 100.6 MHz):** \(\delta\) 200.0, 154.9, 151.6, 151.1, 136.9, 135.2, 119.0, 116.1, 61.4, 53.1, 46.6, 41.0, 31.1, 30.7, 25.6, 24.8, 24.3, 24.2, 22.8, 22.5.

**HRMS:** Calcd. for C\(_{20}\)H\(_{30}\)N\(_6\)S: 386.2253, Found: 386.2244.

**I.R. (Thin film):** 3211, 3038, 2929, 2852, 1567, 1503, 1442, 1329, 1264, 1108 cm\(^{-1}\).
2-(allyl(9H-purin-6-yl)amino)-N-cyclohexylethanethioamide 2b

\[
\begin{align*}
\text{C}_{16}\text{H}_{22}\text{N}_{6}\text{S} \\
\text{Mol. Wt.} = 330.451\text{g.mol}^{-1}
\end{align*}
\]

This compound was synthesized according to the general procedure, using formaldehyde (75 µl, 1.0 mmol), allylamine (75 µl, 1.0 mmol), 6-mercaptopurine (152 mg, 1.0 mmol) and cyclohexyl isocyanide (125 µl, 1.0 mmol). The desired product was isolated in 75% yield (250 mg, 0.756 mmol) after purification by flash column chromatography on silica gel using (80:20 Diethyl ether/ Dichloromethane) as eluent.

**Nature:** Orange solid

**M.P.** = 158.5-159.4°C

**Rf:** 0.2 (60:40 Ethyl acetate/ Dichloromethane)

**NMR** $^1\text{H} (\text{CDCl}_3, 400 \text{ MHz})$: $\delta$ 9.70 (br s, 1H, NH), 8.45 (s, 1H), 8.04 (s, 1H), 5.97 (ddt, $J = 16.3, 10.6, 5.5$ Hz, 1H), 5.31-5.24 (m, 2H), 4.98-4.85 (m, 4H), 4.35-4.28 (m, 1H), 1.98-1.95 (m, 2H, H-Cy), 1.64-1.57 (m, 3H, H-Cy), 1.43-1.33 (m, 2H, H-Cy), 1.25-1.17 (m, 3H, H-Cy).

**NMR** $^{13}\text{C} (\text{CDCl}_3, 100.6 \text{ MHz})$: $\delta$ 196.4, 154.4, 151.3, 150.9, 137.7, 132.4, 119.2, 118.2, 59.5, 53.8, 51.9, 31.1, 25.5, 24.4.

**HRMS:** Calcd. for C$_{16}$H$_{22}$N$_6$S: 330.1627, Found: 330.1623.

**I.R. (thin film):** 3200, 3040, 2928, 2852, 1577, 1515, 1415, 1330, 1261, 1107 cm$^{-1}$. 
**N-Cyclohexyl-2-((2-methoxyethyl)(9H-purin-6-yl)-amino)ethanethioamide 2c**

\[
\text{C}_{16}\text{H}_{24}\text{N}_{6}\text{OS}
\]

Mol. Wt. = 348.466 g.mol\(^{-1}\)

This compound was synthesized according to the general procedure, using formaldehyde (75 µl, 1.0 mmol), 2-methoxyethylamine (86 µl, 1.0 mmol), 6-mercaptopurine (152 mg, 1.0 mmol) and cyclohexyl isocyanide (125 µl, 1.0 mmol). The desired product was isolated in 38% yield (134 mg, 0.384 mmol) after purification by flash column chromatography on silica gel using (40:60 Ethyl acetate/ Dichloromethane) as eluent.

**Nature:** Brown solid

**M.P.** = 186-187°C

**Rf:** 0.3 (50:50 Ethyl acetate/ Dichloromethane)

**NMR \(^1\)H (CDCl\(_3\), 400 MHz):** \(\delta\) 9.34 (br s, 1H, NH), 8.43 (s, 1H), 8.04 (s, 1H), 4.98 (s, 2H), 4.55-4.43 (m, 2H), 4.39-4.30 (m, 1H), 3.78 (t, \(J = 5.3\) Hz, 2H), 3.37 (s, 3H, OMe), 1.97-1.93 (m, 2H, H-Cy), 1.63-1.55 (m, 3H, H-Cy), 1.41-1.30 (m, 2H, H-Cy), 1.19-1.08 (m, 3H, H-Cy).

**NMR \(^13\)C (CDCl\(_3\), 100.6 MHz):** \(\delta\) 196.9, 154.6, 151.4, 151.2, 137.9, 119.4, 70.7, 61.9, 59.0 (OMe), 53.9, 49.8, 31.1, 25.5, 24.4.

**HRMS:** Calcd. for C\(_{16}\)H\(_{24}\)N\(_6\)OS: 348.1732, Found: 348.1734.

**I.R. (thin film):** 3212, 3090, 2931, 2853, 1580, 1425, 1333, 1298, 1113 cm\(^{-1}\).
This compound was synthesized according to the general procedure, using formaldehyde (75 µl, 1.0 mmol), aminoacetalddehyde dimethyl acetal (108 µl, 1.0 mmol), 6-mercaptopurine (152 mg, 1.0 mmol) and cyclohexyl isocyanide (125 µl, 1.0 mmol). The desired product was isolated in 28% yield (109 mg, 0.287 mmol) after purification by flash column chromatography on silica gel using (80:20 Diethyl ether/ Dichloromethane) as eluent.

**Nature:** White solid

**M.P.** = 199-201°C

**Rf:** 0.3 (70:30 Ethyl acetate/ Dichloromethane)

**¹H NMR (CDCl₃, 400 MHz):** δ 9.31 (br s, 1H, NH), 8.45 (s, 1H), 8.05 (s, 1H), 5.01 (s, 2H), 4.84 (t, J = 4.7 Hz, 1H), 4.42-4.30 (m, 3H), 3.43 (s, 6H, 2 OMe), 1.96-1.93 (m, 2H, H-Cy), 1.63-1.56 (m, 3H, H-Cy), 1.37-1.31 (m, 2H, H-Cy), 1.18-1.10 (m, 3H, H-Cy).

**¹³C NMR (CDCl₃, 100.6 MHz):** δ 196.5, 154.7, 151.0, 138.0, 119.3, 102.9, 62.1, 54.5 (OMe), 53.8, 51.5, 31.1, 25.5, 24.5.

**HRMS:** Calcd. for C₁₇H₂₆N₆O₂S: 378.1838, Found: 378.1842.

**I.R. (thin film):** 3324, 3097, 2929, 2853, 2829, 1579, 1525, 1401, 1267, 1121, 1024 cm⁻¹.
**N-cyclohexyl-2-((2-methoxyethyl)(9H-purin-6-yl)amino)-4-methylpentane-thioamide 2e**

![Chemical Structure](image)

**C$_{20}$H$_{32}$N$_6$OS**

Mol. Wt. = 404,572 g.mol$^{-1}$

This compound was synthesized according to the general procedure, using isovaleraldehyde (108 $\mu$L, 1.0 mmol), 2-methoxyethylamine (86 $\mu$L, 1.0 mmol), 6-mercaptopurine (152 mg, 1.0 mmol) and cyclohexyl isocyanide (125 $\mu$L, 1.0 mmol). The desired product was isolated in 70% yield (287 mg, 0.709 mmol) after purification by flash column chromatography on silica gel using (20:80 Ethyl acetate/ Dichloromethane) as eluent.

**Nature:** Pale white solid

**M.P.** = 184.2°C

**Rf:** 0.3 (40:60 Ethyl acetate/ Dichloromethane)

**NMR $^1$H (CDCl$_3$, 400 MHz):** δ 10.32 (br s, 1H, NH), 8.46 (s, 1H), 8.07 (s, 1H), 6.32-6.30 (m, 1H), 4.39-4.32 (m, 2H), 3.98-3.90 (m, 1H), 3.73-3.65 (m, 2H), 3.37 (s, 3H, OCH$_3$), 2.12-2.06 (m, 3H), 1.79-1.66 (m, 2H), 1.57-1.50 (m, 3H), 1.44-1.28 (m, 3H), 1.23-1.05 (m, 2H), 0.93 (d, $J = 6.4$ Hz, 3H), 0.83 (d, $J = 5.7$ Hz, 3H).

**NMR $^{13}$C (CDCl$_3$, 100.6 MHz):** δ 200.1, 155.1, 151.4, 151.3, 137.1, 119.3, 70.1, 61.4, 58.9 (OCH$_3$), 53.2, 43.0, 40.9, 31.0, 30.6, 25.6, 24.9, 24.3, 24.2, 22.8, 22.6.

**HRMS:** Calcd. for C$_{20}$H$_{32}$N$_6$OS: 404.2358, Found: 404.2372.

**I.R. (thin film):** 3209, 3040, 2927, 2861, 1567, 1500, 1434, 1333, 1290, 1103 cm$^{-1}$. 
This compound was synthesized according to the general procedure, using isovaleraldehyde (108 µl, 1.0 mmol), 2-methoxyethylamine (86 µl, 1.0 mmol), 6-mercaptopurine (152 mg, 1.0 mmol) and tert-butyl isocyanide (113 µl, 1.0 mmol). The desired product was isolated in 58% yield (221 mg, 0.583 mmol) after purification by flash column chromatography on silica gel using (30:70 Ethyl acetate/ Dichloromethane) as eluent.

**Nature:** White solid

**M.P.** = 168-169°C

**Rf:** 0.3 (60: 40 Ethyl acetate/ Dichloromethane)

**NMR **$^1$H (CDCl₃, 400 MHz): δ 10.26 (br s, 1H, NH), 8.46 (s, 1H), 8.06 (s, 1H), 6.27-6.24 (m, 1H), 4.61-4.25 (m, 1H), 4.13-3.83 (m, 1H), 3.74-3.58 (m, 2H), 3.37 (s, 3H, OCH₃), 2.18-1.94 (m, 2H), 1.54-1.42 (m, 1H), 1.47 (s, 3H), 0.92 (d, $J = 6.5$ Hz, 3H), 0.81 (d, $J = 4.9$ Hz, 3H).

**NMR **$^{13}$C (CDCl₃, 100.6 MHz): δ 200.5, 155.0, 151.7, 151.3, 136.9, 119.2, 69.9, 62.1, 58.9 (OCH₃), 55.3, 42.4, 40.7, 27.2, 24.8, 22.9, 22.6.

**HRMS:** Calcd. for C$_{18}$H$_{30}$N$_6$O$_5$: 378.2202, Found: 378.2209.

**I.R. (thin film):** 3241, 3052, 2957, 2824, 1568, 1500, 1464, 1433, 1257, 1212, 1099 cm$^{-1}$. 

$N$-(tert-buty)-2-((2-methoxyethyl)(9H-purin-6-yl)amino)-4-methylpentanethioamide 2f

![Chemical structure](image)
**N-cyclohexyl-2-((2-methoxyethyl)(9H-purin-6-yl)amino)-4-phenylbutanethioamide 2g**

![Chemical Structure](image)

**C₂₄H₃₂N₆OS**

Mol. Wt. = 452.615 g.mol⁻¹

This compound was synthesized according to the general procedure, using hydrocinnamaldehyde (146 µl, 1.0 mmol), 2-methoxyethylamine (86 µl, 1.0 mmol), 6-mercaptopurine (152 mg, 1.0 mmol) and cyclohexyl isocyanide (125 µl, 1.0 mmol). The desired product was isolated in 40% yield (185 mg, 0.408 mmol) after purification by flash column chromatography on silica gel using (60:40 Diethyl ether/ Dichloromethane) as eluent.

**Nature:** White solid

**M.P. = 125-126°C**

**Rf:** 0.7 (80:20 Ethyl acetate/ Dichloromethane)

**NMR ¹H (CDCl₃, 400 MHz):** δ 10.35 (br s, 1H, NH), 8.46 (s, 1H), 7.99 (s, 1H), 7.20-7.17 (m, 2H), 7.13-7.08 (m, 3H), 6.15-6.06 (m, 1H), 4.45-4.35 (m, 2H), 4.06-4.00 (m, 1H), 3.70 (dt, J = 15.9, 7.6 Hz, 2H), 3.36 (s, 3H, OMe), 2.70-2.62 (m, 3H), 2.54-2.39 (m, 1H), 2.17-2.03 (m, 1H, H-Cy), 1.82-1.68 (m, 2H, H-Cy), 1.59-1.52 (m, 2H, H-Cy), 1.47-1.25 (m, 3H, H-Cy), 1.22-1.06 (m, 2H, H-Cy).

**NMR ¹³C (CDCl₃, 100.6 MHz):** δ 199.5, 155.1, 151.6, 151.3, 141.1, 136.9, 128.5, 128.3, 126.0, 119.5, 70.1, 62.4, 58.9 (OCH₃), 53.3, 43.2, 33.9, 32.4, 31.1, 30.7, 25.6, 24.4, 24.3.

**HRMS:** Calcd. for C₂₄H₃₂N₆OS: 452.2358, Found: 452.2360.

**I.R. (thin film):** 3212, 3025, 2929, 2852, 1572, 1498, 1452, 1336, 1260, 1114 cm⁻¹.
2-(allyl\(9\text{H}-\text{purin-6-yl})\text{amino})-N\text{-cyclohexyl-4-phenylbutanethioamide} 2h

\[
\text{C}_{24}\text{H}_{30}\text{N}_6\text{S} \\
\text{Mol. Wt. = 434.600 g.mol}^{-1}
\]

This compound was synthesized according to the general procedure, using hydrocinnamaldehyde (146 µl, 1.0 mmol), allylamine (75 µl, 1.0 mmol), 6-mercaptopurine (152 mg, 1.0 mmol) and cyclohexyl isocyanide (125 µl, 1.0 mmol). The desired product was isolated in 47% yield (204 mg, 0.469 mmol) after purification by flash column chromatography using (20:80 Diethyl ether/ Dichloromethane) as eluent.

**Nature:** White solid

**M.P. =** 162.6°C

**Rf:** 0.7 (60:40 Ethyl acetate/ Dichloromethane)

**NMR \textsuperscript{1}H (CDCl\textsubscript{3}, 400 MHz):** \(\delta\) 10.46 (br s, 1H, NH), 8.46 (s, 1H), 7.99 (s, 1H), 7.22-7.18 (m, 2H), 7.15-7.09 (m, 3H), 6.26-5.98 (m, 2H), 5.24 (d, \(J = 17.4\) Hz, 1H), 5.11 (d, \(J = 10.3\) Hz, 1H), 5.00-4.81 (m, 1H), 4.72-4.56 (m, 1H), 4.36-4.34 (m, 1H), 2.66-2.60 (m, 3H), 2.54-2.37 (m, 1H), 2.07-2.06 (m, 1H, H-Cy), 1.77-1.70 (m, 2H, H-Cy), 1.59-1.50 (m, 2H, H-Cy), 1.45-1.31 (m, 3H, H-Cy), 1.23-1.06 (m, 2H, H-Cy).

**NMR \textsuperscript{13}C (CDCl\textsubscript{3}, 100.6 MHz):** \(\delta\) 199.2, 154.8, 151.7, 151.3, 141.2, 136.6, 135.1, 128.5, 128.4, 126.0, 119.0, 116.2, 62.7, 53.2, 46.6, 33.9, 32.4, 31.1, 30.7, 25.6, 24.4, 24.3.

**HRMS:** Calcld. for C\textsubscript{24}H\textsubscript{30}N\textsubscript{6}S: 434.2253, Found: 434.2255.

**I.R. (thin film):** 3218, 3024, 2930, 2852, 1570, 1499, 1435, 1332, 1299, 1265 cm\(^{-1}\).